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# IMMUNITY AND THE POWER OF DIGESTION.[1]

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The proteins are the fundamental chemical constituents of the living protoplasm in all our tissues and organs. But the cells of the tissues do not take up the proteins as such, they are known to live on the products of protein digestion, on their building stones, the various amino-acids. And by a long process of synthetic character the cells of a multicellular organism build up out of these building stones their own individual proteins of a highly specific structure.

The multicellular organism possesses special organs of digestion which successfully perform the work of splitting the ingested food to the stage of amino-acids, in which stage they become capable of passing through the intestinal wall; they are absorbed here and transported to all our tissues, which in this manner are provided with various substances for their synthetic work in order to replace the wear and tear of the living substance during adult life or to build up organs and tissues during developmental stages.

Now are the cells of all our organs and tissues which, under usual conditions, are supplied for their synthetic work with ready made building stones, without one of the most characteristic and important properties of the living matter, viz., the power of splitting the chemically more complex proteins to the stage of amino-acids? Or are these cells not manifesting a digestive potency inherent in them, because they have no chance of manifesting it, because the ingested food does not reach them primarily and undergoes the hydrolytic changes before it is capable of being absorbed? Is it a lack of power or a lack of opportunity which prevents the cells of our tissues from manifesting a digestive capacity under usual conditions?

[1] Given at the meeting of the Section of Biology, New York Academy of Sciences, October 13, 1919.

A most wonderful property exhibited by the tissues themselves is to inhibit growth of foreign tissue. This resistance of the organism against proliferation of any heterogeneous cellular elements, be it normal tissues, tumor cells or microörganisms, is more generally known under the term of immunity. There is little need to emphasize the importance of any new information concerning this problem. Disregarding, however, the most earnest efforts and attempts to throw upon this property light sufficient to master it, no definitive knowledge has yet been acquired concerning the nature of this property.

In all organisms, plants and animals as well, the power of resistance against proliferation of any foreign tissue does not seem to depend upon the activity of a special organ in the organism. A graft of heterogeneous tissue simply does not take, a tumor graft does not grow, microörganisms do not proliferate, die and disappear in an immune or immunized animal. A living cell endowed with the faculty of proliferation, for example, a tumor cell, well known for its high rate of proliferation and on account of this property disastrous to the organism, on which it has settled, if grafted on an immune organism, will certainly find here all of the elements needed for the building up of its own protoplasm, for we know that the tissues of the organism are abundantly provided with various amino-acids, and these not being specific, can be used equally well by any tissue. And still a tumor cell will not live on an immune organism. It dies and disappears.

If now we inquire into the relation between the digestive power of the cell and resistance in a unicellular organism, we will see that both phenomena in this case are very closely connected. A unicellular organism can ingest another living organism, bacteria as well and the latter, while within a cytoplasmic vacuole of the former, are killed and consecutively digested by the enzymes of the phagocyte. The unicellular organism in this case proves to be immune against a possible intracytoplasmic proliferation of the ingested living individual, primarily and solely because of its digestive capacity.

The question whether in a multicellular organism any relation exists between its resistance against proliferation of a foreign tissue in it and a digestive power of its tissues is obscured by the

fact that the tissues of the organism do not exercise under normal conditions any digestive power, and it is not definitely settled, which of the various tissues, if any, besides those connected with the digestive tract, are endowed with a digestive power. And still there exist sufficient indications that the tissues of a multicellular organism, besides those highly specialized of the digestive tract, are equipped with enzymes which confer on them a digestive power similar to that so characteristic of the special elements in the digestive tract. If the tissues of a multicellular organism be put under the stress of starvation, under which condition no amino-acids will reach them from the absorbing surface of the digestive tract, the tissues will in this case use up tissue proteins, they themselves hydrolyze the proteins or digest them, which work is made possible by the presence of enzymes in these cells. And another example of digestive work performed by tissue cells of a multicellular organism can be found in the growth of tissue on artificial media. Here again the transplanted bits of tissue do not find within the culture medium ready building stones for the building up of their protoplasm in the form of amino-acids, but only proteins of the blood plasma clot. Here again the cells of the tissues themselves have a chance of performing the splitting or digestion of the proteins, and they do it. In both these cases we base our conclusions of the presence of enzymes in the tissue cells on the results of the experiments: on the continuation of the output of nitrogen by the organism during a diet free from nitrogen in the starvation experiment, and on the further growth of the tissue in the culture experiment. The fact only not the mechanism of the digestive activity by tissue cells is determined in both cases.

Some information concerning the mechanism, or rather concerning one of the mechanisms, by which cells of our body may digest, *i.e.*, split and assimilate protein may be gained by microscopical study. And this study informs us that in embryos developing from mesoblastic eggs, *i.e.*, from eggs containing great quantities of yolk, as for example, from birds eggs, all of the tissues contain at an early stage a great quantity of yolk granules in their cytoplasm, which are digested intracellularly and assimilated. Endodermal cells as well as ectoderm and mesoderm cells, even primitive germ cells, all are endowed with

an intracellular digestive capacity. And this capacity is surely not lost during the development of the embryo, at least the mesenchymal cells continue to exercise this faculty, and wherever cells in the developing organism have lost their normal correlation with other tissues, as for example, red blood corpuscles during the rearrangement of vessels, mesenchymal cells are seen to ingest them and digest them within their cytoplasm. The mechanism of this digestive activity is analogous to that observed in unicellular organisms. Enzymes are not given off as in the digestive tract, they work within the cytoplasm, they are endoenzymes. To a digestive activity of the mesenchymal cells is due the disappearance of aseptic emboli, trombi and infarcts; small sequesters may be entirely resorbed and catgut sutures disappear in the organism in a short time.

An intracellular digestive activity is exhibited in an intense way by the tissues of embryos developing from mesoblastic eggs in the early stages of embryonic development and only occasionally during adult condition. This power is dormant in the tissues of mammals during embryonic development, the embryo receiving all the materials needed for its development in the form of amino-acids from the maternal placenta, but is awakened at the first opportunity of being confronted with unsplit protein.

The digestive power of the tissues is well evident in respect to cellular protein in the dead form. Only in a unicellular organism did we see that their digestive activity confers on them a power over living organisms and cells as well and therefore becomes the source and the cause of their immunity against a possible proliferation of the ingested organisms. May the digestive capacity of the tissues of a multicellular organism, of which we have seen a few examples, be also in some way connected with the failure of a heterogeneous graft to take? Is this power not the deleterious factor which cannot be overcome by the grafted heterogeneous tissue and which inhibits its growth and proliferation?

The results of a long series of experiments, which I am going to illustrate, show without any doubt that at least in some cases it is the digestive activity of an adult mesenchymal cell which inhibits the growth of a heterogeneous tumor or rather destroys the actively growing tumor. The experiments were made with

different tumors, but only the Ehrlich sarcoma, and the tumor known at the Crocker Fund Laboratory, under the number 180, gave demonstrable results. It is known that mammalian tumors may be grown easily on chick embryos, but not on adult animals. Also normal adult chick tissue grows well on embryos of the same species. Therefore, embryonic tissues, more particularly the chick allantois, have been used by me as a culture medium, to bring together mammalian tumors and various adult chick tissues. It was expected that the study of the interaction of the tissues of the adult naturally immune fowl and of the mammalian tumor cells grown in a culture medium, for both equally favorable, might show whether the digestive capacity of the tissues more particularly that of the adult splenic mesenchymal cells may in any way be connected with the resistance offered by the adult animal to the grafting of the tumor on it. The experiments have shown that the Ehrlich sarcoma gives invariably a good growth if grafted alone, but if grafted in a mixture with the spleen, disappears even after a short period of proliferation. The short-lived fame of the small lymphocytes thought to be responsible for this disappearance is still in our memory. Only an absolute disregard of microscopical findings can explain how microscopical pictures similar to those shown here (Figs. 1, 2, 3 and 4), have been overlooked and how the small lymphocyte could become the fetish of the immunity.

Microscopical preparations, as seen in retouched photographs, which accompany this paper, illustrate in a striking way the process of disappearance of tumor foci surrounded by the adult splenic mesenchyme in the allantois. Two lines of activity are observed in the mesenchyme, it splits off numerous mobile cells of hemoblastic nature which differentiate further into granular leucocytes. This developmental potency is exhibited in an even more intensive way by the splenic adult mesenchyme, if the splenic tissue is grafted alone on the chick allantois. But the fact of grafting the splenic tissue together with tumor reveals in it a new potency and this is its power of isolating and surrounding tumor cells, of enclosing them in vacuoles and of digesting them within these vacuoles (Figs. 1, 2, 3 and 4). The adult splenic mesenchymal cell is apparently attracted toward the mammalian tumor cell. Contrary to the embryonic mesen-

chyme, the adult mesenchymal cells, once close to the tumor cell, will not indifferently pass by, but together with other mesenchymal cells, will tightly surround it. The tumor cell, in response to the approach of the adult mesenchymal cell, withdraws its cytoplasmic processes, becomes immobile and assumes soon a spherical shape. The Figure 1 illustrates a tumor focus in which the cells still intensely proliferate in the center as may be seen from numerous mitoses present. The tumor focus is however surrounded by a zone of mesenchymal syncytium of splenic origin. The cells of this tissue encircle the tumor cells at first surrounding them very tightly (Figs. 1 and 2, *x*). The adult splenic mesenchymal cells of the fowl treat a heterogeneous mammalian tumor cell, which, if present alone in the embryonic allantois, would live and proliferate in no other manner than if it were a block of dead protein. They gather around the tumor cells and enclose them into a capsule and then secrete a fluid within the little cavity occupied by the tumor cell. The nature of this fluid is such that a disintegration of the tumor cell takes place and a complete splitting of its proteins, it must therefore contain proteolytic enzymes. The tumor cell gradually loses its structure (*Tc'*, Figs. 1, 2, 3 and 4) is transformed into a block of structureless protein (*Tc''*, Figs. 1, 2, 3 and 4) and finally disappears completely. Tumor cell after tumor cell is digested in this manner. In the case of the Ehrlich sarcoma, the rate of digestion of the tumor cells by the splenic mesenchyme is higher than the rate of proliferation of the tumor cells, and the grafted tumor, even after a good start of development, disappears. The same process is observed in relation to the sarcoma 180. Only in this case the rate of proliferation of these tumor cells is higher than the rate of their digestion by the splenic mesenchyme, and the tumor still grows in spite of the existence of a peripheral zone around it, in which the process of digestion of tumor cells by mesenchymal cells is most evident.

The study of microscopical preparations allows us to follow the gradual changes which the tumor cells undergo within the vacuoles surrounded by mesenchymal cells, changes which lead to the full disappearance of the tumor cells. Figures 2, 3 and 4 show very clearly how healthy tumor cells *H Tc* are cut off from the tumor focus, the tumor cells withdrawing their processes

and rounding up, how the tumor cells gradually lose their structure *Tc'*, their cytoplasm becoming vacuolized, their nuclei pycnotic and how finally the tumor cells disappear entirely.

Now in respect to the small lymphocytes, may they not be still connected in some indirect way with the disappearance of the tumor cells? Round-cell infiltration has been described around the disappearing tumor grafts within the allantois. But though the small lymphocyte is a round cell, not every round cell is a small lymphocyte. Round cell infiltration exists indeed around such grafts. This infiltration, however, at a closer study proves to consist not of small lymphocytes, but of round, mobile cells of hemoblastic nature which, as mentioned above, differentiate into granular leucocytes. As has been shown in one of my previous papers, the small lymphocytes are not very viable in the allantois and in most cases quickly disappear in the grafted splenic tissue.

It is a positive tropism between the adult mesenchymal cell and the tumor cell expressed in the phagocytic power of the mesenchymal cell over the tumor cell and the digestive activity of the adult mesenchymal cell which prove to be the direct factors in the disappearance of the tumor cells in a double mixed graft of tumor and spleen. One of the remarkable results of the various experiments undertaken in this direction is the fact, that only the adult splenic mesenchyme, not the embryonic, exhibits the capacity of digesting tumor cells. This observation well corresponds with the fact that the embryo fails to resist growth of heterogeneous tissue.

I have already mentioned that only in respect to the Ehrlich sarcoma and to the sarcoma 180 could I obtain results which clearly demonstrate the phagocytic and digestive activity of the adult splenic mesenchymal cells. The study of the growth of other tumors and of the check of their growth is sufficiently advanced to enable me to conclude that the inhibition of the carcinoma growth is effected by a mechanism not altogether identical to that described in relation to the Ehrlich sarcoma cells. Must this fact astonish us? I do not think so. To expect a literally identical response of the mesenchymal cells to different agents would be just as inconsistent as to expect the digestive activity in all multicellular animals to proceed in a perfectly identical

manner. And we know that this is not the case. We know that in multicellular organisms there exists a digestive cavity, into which free enzymes are poured, we know, however, that in sea-anemones, though a digestive cavity does exist, no ferments had ever been discovered in it and the digestion of the food proceeds through the immediate apposition to it of definite cellular elements.

The fact that at least in some cases the phagocytic and digestive activity of the mesenchymal adult cells is found to be the deleterious factor, which cannot be overcome by some of the tumors and which inhibits the growth of these tumors, or rather destroys an actively growing tumor, throws a new light on the immunity problem in general, since the power of resistance against proliferation of foreign tissue, though manifested in different ways, can certainly not be of a fundamentally different nature.

## EXPLANATION OF FIGURES.

The figures are retouched photographs from original preparations. The Figure 1 at about 400, the Figure 3, 700 and the Figures 2 and 4, 1000 diameters.

### Abbreviations.

*Gr Lc.* Granular leucocytes.
*H Tc.* Healthy tumor cells.
*S Ms.* Splenic mesenchyme exercising a phagocytic and digestive activity.
*Tc'.* Tumor cells in various stages of disintegration.
*Tc''.* Tumor cells transformed into blocks of almost structureless protein.
*V.* Vessel.
*X.* Tumor cells tightly surrounded by mesenchymal cells.

The figures illustrate the result of growth of mixed grafts, consisting of mammalian tumor and adult chick spleen on the allantois.

### Plate I.

Fig. 1. Actively growing tumor focus of 4 days growth in the allantois. In the center groups of healthy tumor cells with numerous mitoses. The focus of healthy tumor tissue is surrounded by a zone in which the splenic mesenchymal cells encircle the tumor cells and digest them in closed vacuoles.

Fig. 2. Small area of the peripheral zone around a tumor focus of 4 days growth. Only two tumor cells (*H Tc*) still exhibit a healthy structure. All the others (*Tc'* and *Tc''*) show various changes dependent upon the digestive activity of the splenic mesenchymal syncytium enclosing them in vacuoles.

FIG .1.

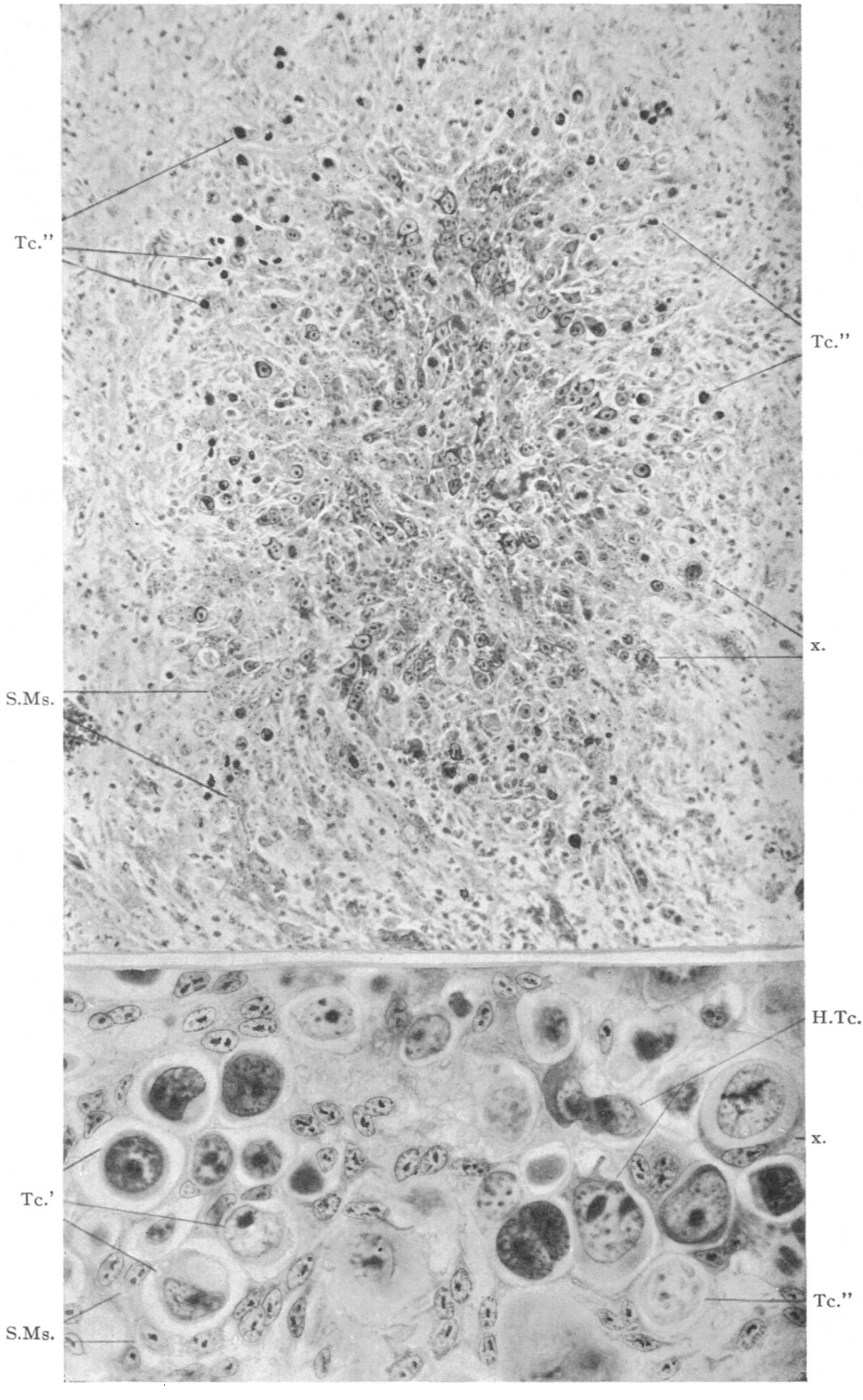


FIG. 2.

PLATE II.

FIG. 3. Small region of the peripheral zone around a tumor focus of 4 days growth, showing a group of healthy tumor cells (*H Tc*) and numerous other tumor cells in various stages of disintegration.

FIG. 4. Small area of the peripheral zone around a tumor focus of 4 days growth, illustrating the disintegration of the tumor cells within the vacuoles, formed by the splenic mesenchymal cells.

FIG. 3.

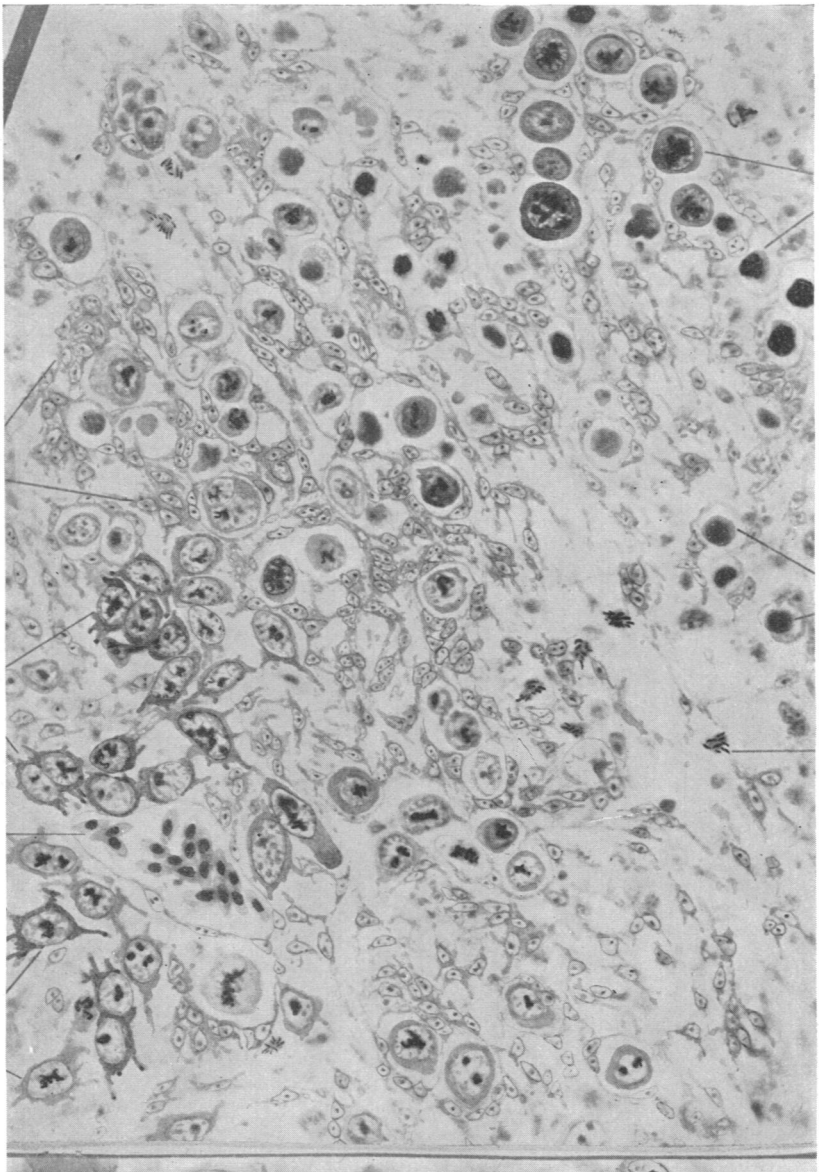


FIG. 4.